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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

OMMY

| Applicant's or agent's file reference<br>ZRC-NDDS-003 | **FOR FURTHER ACTION** See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
|---|---|---|
| International application No.<br>PCT/IN 03/00229 | International filing date *(day/month/year)*<br>25.06.2003 | Priority date *(day/month/year)*<br>26.06.2002 |
| International Patent Classification (IPC) or both national classification and IPC<br>A61K9/00 | | |
| Applicant<br>CADILA HEALTHCARE LIMITED et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 21.01.2004 | 05.10.2004 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Sindel, U<br>Telephone No. +49 89 2399-7064 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IN 03/00229

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-16 as originally filed

**Claims, Numbers**

1-22 received on 17.05.2004 with letter of 10.05.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

**see separate sheet**

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 17

   because:

   ☒ the said international application, or the said claims Nos. 17 relate to the following subject matter which does not require an international preliminary examination (specify):

   **see separate sheet**

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 3-4 |
| | No: | Claims | 1-2, 5-23 |
| Inventive step (IS) | Yes: | Claims | - |
| | No: | Claims | 3-4 |
| Industrial applicability (IA) | Yes: | Claims | 1-23 |
| | No: | Claims | - |

2. Citations and explanations

   **see separate sheet**

Reference is made to the following documents:

D1: WO 00/38650
D2: US 5 232 704

The Applicant is informed that there exists an intermediate document which might become relevant in the European Phase of the application. The intermediate document is WO 03/035029 having a priority of 25.10.2001, a date of filing of 25.10.2002 and a publication date of 1.05.2003.

**Item I**

The new set of claims submitted with letter of 10.05.2004 does not fulfill the requirements of Article 19(2) PCT since the amendments go beyond the disclosure as filed.
New claim 1 limits the pharmaceutical excipients used in the first layer to a mixture consisting of (I) polymers selected from ethylcellulose or suitable enteric polymers of cellulose derivatives and (ii) hydrogenated oils, waxes, fatty acids either alone or in combination. Since there is no basis for this amendment in the description, the report is established according to Rule 70.2© PCT as if the amendments have not been made.

**Item III**

Claim 17 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Item V**

1) Novelty
The subject matter of claims 1-2 and 5-23 is not regarded as new in the sense of Article 33(2) PCT.

D1 already describes a bilayer tablet adapted for gastric retention consisting of a first layer of a water-soluble polymer like e.g. polyethylene oxide or cellulose derivatives and a second layer comprising an active agent like acyclovir and a hydroattractant like e.g. cellulose derivatives or cross-linked polyacrylic acid (see claims 1-4).

2) Inventive step
The subject matter of claims 3-4 does not involve an inventive step in the sense of

Article 33(3) PCT.

The problem to be solved in the present application is the provision of an alternative bilayer formulation adapted for gastric retention.
The solution provided is a bilayer delivery system with a first buyoant or floating layer comprising ethylcellulose and hydrogenated oil.

Closest prior art is D2 describing a bilayer formulation for gastric retention comprising a drug release layer and a buoyant or floating layer (see abstract). The latter consists of hydrocolloids of high viscosity like hydroxypropyl methylcellulose, other cellulose derivatives, gums, polysaccharides and gelatin (see column 6, lines 14-18).

Choosing different excipients but having the same characteristics does not involve an inventive step unless there is not a surprising effect of this special combination. In such a case this unexpected effect should be shown in comparison trials with the prior art.

3) Industrial applicability
The subject matter of claims 1-16 and 18-23 is industrially applicable in the sense of Article 33(4) PCT.

For the assessment of the present claim 17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Claims:**

We claim

1. A pharmaceutical gastro-retentive delivery system for controlled release of therapeutically active agent in stomach or upper part of gastro-intestinal tract in the form of bilayer dosage form which comprises,
   a) One layer (layer-A) which is responsible for retaining the dosage form in stomach or upper part of gastro-intestinal tract (spatial control) for a prolonged period, comprising of pharmaceutical excipients having low bulk density, optionally with other pharmaceutical aids.
   b) Second layer (Layer- B) which is responsible for prolonged or controlled drug delivery (temporal control) of therapeutic agent which comprises of the active agent and controlled release matrix polymers optionally with other pharmaceutical aids.
2. The delivery system as claimed in claim 1, wherein said pharmaceutical excipients with low bulk density is selected from cellulosic derivatives either natural, semi-synthetic or synthetic, polyethylene oxide, fatty acids, hydrogenated oils, waxes and shellac, either alone or in combination thereof.
3. The delivery system as claimed in claim 1(a) above, wherein said pharmaceutical excipient with low bulk density is ethyl cellulose in combination with hydrogenated oils.
4. The delivery system as claimed in any preceding claims wherein the ratio of ethylcellulose and hydrogenated oils is in the range of 95:5 to 30:70.
5. The delivery system as claimed in claim 1(a) above, wherein said pharmaceutical aids are pharmaceutical lubricants, antiadherents and glidants.
6. The pharmaceutical aids as claimed in claim 5, is selected from magnesium stearate, talc, colloidal silicon dioxide, stearic acid, magnesium stearate fumerate, glyceryl behenate and hydrogenated oils or combination thereof.
7. The delivery system as claimed in claim 1 (b) above, wherein said controlled release matrix polymers is selected from synthetic or semisynthetic cellulose derivatives like hydroxypropyl methylcellulose, ethylcellulose, hydroxypropylcellulose, methylcellulose, sodium carboxymethylcellulose, natural polymers such as xanthan gum, gelatin, synthetic polymers, acrylic acid derivatives and polyvinyl acetate or mixtures thereof.



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8. The delivery system as claimed in claim 1(b) above, wherein said pharmaceutical aids are selected from group of pharmaceutical fillers, disintegrants, lubricants, binders, antiadherents and glidants or combinations thereof.
9. The pharmaceutical disintergrant as claimed in claim 8 is selected from crosslinked polyvinylpyrrolidone, crosslinked sodium carboxymethyl cellulose, sodium starch glycolate, microcrystalline cellulose, starch, and pregelatinized starch or their combinations.
10. The pharmaceutical binders as claimed in claim 8 is selected from natural polymers selected from starch or gum including acacia, tragacanth, gelatin or synthetic polymers selected from polyvinyl pyrrolidone, methyl cellulose, ethyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose.
11. The pharmaceutical antiadherents, glidants and lubricants as claimed in claim 8 is selected from magnesium stearate, talc, colloidal silicon dioxide, stearic acid, salts of stearic acid, magnesium stearate fumarate, glyceryl behenate and hydrogenated oils.
12. The drug delivery system as claimed in claim 1, wherein said therapeutically active agent may be in the form of a raw powder, dispersed or embedded in a suitable liquid, semisolid, micro- or nanoparticles, micro- or nanospheres, a tablet, a caplet, or in a suitable processable form.
13. The delivery system as claimed in claim 1, wherein said therapeutically active agent is a drug having a narrow absorption window in the gastrointestinal tract.
14. The delivery system as claimed in claim 1, wherein said therapeutically active agent is selected from the group consisting of therapeutic, chemotherapeutic, antibiotic antidiabetic, anti-cancers, anti-fungals, anti-filarial, antiviral agents, lipid lowering agents, analgesics, non-steroidal anti-inflammatory agents, anti-ulcer agents, anti-epileptics, anti-gout, immunosuppressants, drugs for respiratory therapy, dopaminergic agents, skeletal muscle relaxants, cardiovascular agents, antipsychotics or those drugs which does not show uniform absorption characteristic throughout the length of the gastrointestinal tract.
15. The delivery system as claimed in claim 1, wherein said therapeutically active agent may also be a drug for local treatment of the gastrointestinal tract.
16. The delivery system as claimed in claim 1, wherein said therapeutically active agent is selected from antibacterial/anti-infective agents, such as ofloxacin, ciprofloxacin,



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cefuroxime, cefatrizine, cefpodoxime, clarithromycin, loracarbef, azithromycin, cefadroxil, cefixime, amoxycillin; antivirals, such as acyclovir; cardiovascular agents, such as diltiazem, captopril; lipid lowering agents such as simvastatin, lovastatin, atorvastatin; non-steroidal anti-inflammatory agents such as etodolac, ketorolac; anti-ulcer agents such as ranitidine, famotidine; drugs for respiratory diseases, such as fexofenadine, pseudoephedrine, phenylpropanolamine, dextromethorphan, chlorpheniramine; dopaminergic agents, such as bromocriptine; immunosuppressants, such as cyclosporin; skeletal muscle relaxants, such as baclofen; anti-gout agents, such as allopurinol; antidiabetic agents such as acarbose, glipizide.

17. Use of the delivery system as claimed in claim 1, for treatment of disease conditions as described in any preceding claims above..
18. The delivery system as claimed in any preceding claims wherein the layers A & B are prepared by technique selected from melt granulation, wet granulation or direct compression.
19. The delivery system as claimed in any preceding claims wherein the amount of therapeutically active agent is present in an amount ranging from about 0.2 to 1000 mg.
20. The delivery system as claimed in 1 wherein the dosage form floats on the surface of the gastric fluid for prolonged period ranging from 0.5 to 10 hours.
21. The delivery system as claimed in any preceding claims which may be optionally coated with rapidly dissolving water soluble film forming polymer or rapidly dissolving pharmaceutical excipient.
22. A drug delivery system as claimed in any preceding claims which includes tablets, caplets or tablets filled in capsules..
23. A pharmaceutical composition prepared according to the present invention suitable for human composition.

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